increase in natural abundance ^{2}H would result in only 1% of protons in fatty acids from the ketogenic diet to be replaced by ^{2}H. The kinetic isotope effect (KIE) as referred to by Boros et al would reduce rates of enzymatic reactions breaking carbon-deuterium bonds. As such, the presumed high deuterium content of our ketogenic diet as suggested by Boros et al would slow down ketone body metabolism via KIEs on ketolytic enzymes yet also produce deuterated metabolic water. The extent of ketone body metabolism is exactly what we measured in vivo with ^{13}C MR spectroscopy. In contrast to what Boros et al suggest, the relative rate of ketone body oxidation was similar between tumorous and nontumorous brain tissue, and was *increased* when animals were put on the ketogenic diet (Supplementary Table 2).[1] Interestingly, if the level of the elusive deuterated water was indeed high, if anything it could have had a tumor growth–inhibiting effect, as observed by Rodrigues et al after providing 50% (v/v) $^{2}H_2O$ for 9 days in glioma-bearing rats (which is several orders of magnitude above the ^{2}H enrichment anticipated from a diet with slightly increased ^{2}H content).[2]

Funding

H. M. De Feyter was supported by fellowship 10A087 from the American Institute for Cancer Research, and a 2013 Discovery Award from the American Brain Tumor Association. As a member of the Yale Cancer Center, H. M. De Feyter is supported by NIH grant CA-16359 from the National Cancer Institute.

Henk M. De Feyter, Kevin L. Behar, Robin A. de Graaf, and Douglas L. Rothman

Department of Radiology and Biomedical Imaging, Magnetic Resonance Research Center, Yale University School of Medicine, New Haven, Connecticut (H.M.DeF., R.A.deG., D.L.R.); Department of Psychiatry, Magnetic Resonance Research Center, Yale University School of Medicine, New Haven, Connecticut (K.L.B.); Department of Biomedical Engineering, Yale University, New Haven, Connecticut (R.A.deG., D.L.R.)

Corresponding Author: Henk M. De Feyter. Yale University School of Medicine, Department of Radiology and Biomedical Imaging, 300 Cedar Street, P.O. Box 208043, New Haven, CT 06520-8043 (henk.defeyter@yale.edu).

References

1. De Feyter HM, Behar KL, Rao JU, et al. A ketogenic diet increases transport and oxidation of ketone bodies in RG2 and 9L gliomas without affecting tumor growth. *Neuro-Oncol*. 2016;18(8):1079–1087.
2. Rodrigues TB, López-Larrubia P, Cerdán S. Redox dependence and compartmentation of [13C]pyruvate in the brain of deuterated rats bearing implanted C6 gliomas. *J Neurochem*. 2009;109(S1):237–245.

doi:10.1093/neuonc/now291
Advance Access date 28 February 2017

Comment on: Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection

With great interest we read the article by Wefel et al entitled "Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection,"[1] recently published in *Neuro-Oncology*. We would like to congratulate the authors on their work, as neurocognitive function (NCF) is crucial for our patients' quality of life and is gaining more attention in patient care. Nevertheless, there seem to be some shortcomings in interpreting the data.

Firstly, it is well known that most patients show neurocognitive decline upon diagnosis of both high- and low-grade gliomas.[2,3] It has recently been pointed out that inflammatory reactions, patterns of DNA repair, and metabolism pathways are strongly associated with NCF.[4] In the present study, the authors carried out an analysis separated by mutational status of isocitrate dehydrogenase (IDH) and evaluated the presence of preoperative NCF impairments in correlation with IDH mutation.

Although total lesion volume on fluid attenuated inversion recovery (FLAIR) (including peritumoral edema) was comparable in both groups, the patients' age ($P < .0001$), Karnofsky Performance Index ($P < .0001$), and tumor volume on T1-MRI (without contrast) ($P < .006$) were significantly different. These differences are not corrected for statistically, which greatly limits the strengths of the conclusion. It may well be that the mean age difference of 17 years between the groups affects NCF as a result of reduced neuroplasticity with age.[5,6] The given T1 and FLAIR volumes demonstrated significantly more edema compared with the actual tumor volume for IDH wild-type tumors. We agree that the IDH wild-type tumors may cause a larger, more aggressive infiltration of surrounding brain tissue. Nevertheless, the conclusion that genetic alterations of tumors alter NCF cannot be directly concluded.

Causal research on the origin of NCF impairments is cumbersome and has not yet yielded clear results. Most likely NCF impairment is due to infiltrative behavior of the tumors into subcortical networks,[7] as this has been demonstrated in diffuse infiltrating low-grade gliomas.

With these limitations of current research, the cause of NCF impairments remains largely unclear. The effect of IDH mutational status on NCF is therefore still a matter of debate, as confounding factors like age may play an important role.

We congratulate the authors for their commitment to this crucial topic in the care of patients with gliomas.

Christian F. Freyschlag, Johannes Kerschbaumer, and Claudius Thomé

Department of Neurosurgery, Medical University of Innsbruck, Innsbruck, Austria

Corresponding Author: Freyschlag, C. F., Department of Neurosurgery, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria (christian.freyschlag@i-med.ac.at).

References

1. Wefel JS, Noll KR, Rao G, Cahill DP. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. *Neuro Oncol*. 2016;18(12):1656–1663.
2. Racine CA, Li J, Molinaro AM, Butowski N, Berger MS. Neurocognitive function in newly diagnosed low-grade glioma patients undergoing surgical resection with awake mapping techniques. *Neurosurgery*. 2015;77(3):371–9; discussion 379.
3. Raysi Dehcordi S, Mariano M, Mazza M, Galzio RJ. Cognitive deficits in patients with low and high grade gliomas. *J Neurosurg Sci*. 2013;57(3):259–266.
4. Liu Y, Zhou R, Sulman EP, et al. Genetic modulation of neurocognitive function in glioma patients. *Clin Cancer Res*. 2015;21(14):3340–3346.
5. Kohama SG, Rosene DL, Sherman LS. Age-related changes in human and non-human primate white matter: from myelination disturbances to cognitive decline. *Age (Dordr)*. 2012;34(5):1093–1110.
6. Liu H, Yang Y, Xia Y, et al. Aging of cerebral white matter. *Ageing Res Rev*. 2016. doi:10.1016/j.arr.2016.11.006.
7. Duffau H. The huge plastic potential of adult brain and the role of connectomics: new insights provided by serial mappings in glioma surgery. *Cortex*. 2014;58:325–337.

doi:10.1093/neuonc/now289
Advance Access date 18 February 2017

Reply to Freyschlag et al

We appreciate the commentary of Freyschlag et al regarding our manuscript identifying a clinical neurocognitive phenotype varying on the basis of the mutation status of the isocitrate dehydrogenase (IDH) 1 gene.[1] We agree that identifying and differentiating the specific factor(s) (eg, tumor, edema) that cause neurocognitive dysfunction is challenging, just as identifying the tumor margin from edema can be challenging radiographically. The thoughtful commentary of Freyschlag et al elaborates on several interesting issues in studying neurocognitive function in this patient population.

Several demographic and clinical features, including age and KPS, are highly correlated with IDH1 mutation status. While it may initially seem like a good idea to simply control for these in a statistical model, given multicollinearity between the demographic and clinical features and the tumor mutation status, as well as neurocognitive outcome, this would lead to suppression and reduce the magnitude of the relationship between the predictors and the outcome. As for the specific concern regarding age differences across IDH1 groups, the standardized neurocognitive test scores are age adjusted—thus the difference in neurocognitive performance between the 2 patient samples is unlikely to be due to the difference in age.

Freyschlag et al correctly pointed out that patients with IDH1 wild-type (WT) tumors had smaller T1-weighted but similar fluid attenuated inversion recovery volumes compared with mutant (IDH1-M) tumors. They also had greater and more frequent neurocognitive dysfunction with highly significant associations between neurocognitive function and lesion size—whereas this association was absent in patients with IDH1-M tumors. We have recently published results from our analysis of the brain's gray matter structural connectome in this patient sample that demonstrated patients with IDH1-WT tumor compared with IDH1-M tumor had lower degree and lower network efficiency in several medial frontal, posterior parietal, and subcortical regions.[2] Cognitive reserve mediated the relationship between network efficiency and cognitive dysfunction in patients with IDH1-M tumors but not IDH1-WT tumors. Further, tumor volume was a predictor of cognitive dysfunction in patients with IDH1-WT tumors but not IDH1-M tumors. Again, while ascribing specific causal effects is difficult, we argue that the more rapidly growing IDH1-WT tumor results in greater disruption in the organization of the brain's network topology and greater cognitive dysfunction. Given the increasing interest in both the molecular characterization of tumors and quantitatively and objectively measuring neurocognitive function, we expect there will be larger patient cohorts in the future that will permit investigating the extent to which patient age mediates neuroplasticity, brain connectivity, and neurocognitive function within and between samples of patients with IDH1-WT and IDH1-M tumor.

Importantly, we disagree that the most likely "cause" of neurocognitive impairment is diffuse infiltration into